Remarks

Claims 42, 45, 46 and 51-63 were pending in the subject application. By this Amendment, claims 58 and 59 have been amended, and new claims 64-68 have been added. The undersigned avers that no new matter is introduced by this amendment. Support for the new claims and amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 42, 45, 46, and 51-68 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Submitted herewith is a Request for Continued Examination (RCE) under 37 CFR §1.114 for the subject application.

By this Amendment, claims 58 and 59 have been amended for clarity. Support for this amendment can be found, for example, at page 13, lines 7-13, of the specification. Claims 64-67 have been added. Support for claims 64-67 can be found, for example, at page 11, lines 26-28, of the specification. Support for claim 68 can be found, for example, at page 15, lines 10-15, of the specification.

Claims 42, 45, 46, and 51-63 are rejected under 35 USC §112, first paragraph, as non-enabled by the subject specification. The Examiner acknowledges that the specification enables methods of inhibiting expression of Dengue virus (DV) genes within an isolated mammalian host cell by RNA interference; however, the Examiner asserts that the specification does not enable inhibition of expression of DV genes in a mammalian animal host. The Examiner also asserts that delivery of gene expression vectors *in vivo* was problematic at the time the subject application was filed. Applicants respectfully traverse and submit that the claimed invention is fully enabled by the subject specification.

As an initial matter, the Examiner asserts that one skilled in the art, relying on the teachings of the specification and prior art, would not know to which cells in a mammal an siRNA vector should be delivered. As indicated at page 3, lines 9-12, of the specification, and Examples 8 and 9, at pages 29-30, of the specification, dendritic cells, monocytes and macrophages are susceptible to DV infection. Submitted herewith are Tassaneetrithep B. *et al.*, *J. Experimental Medicine*, 2003,

197(7):823-829, Seema and Jain, *Indian Journal of Clinical Biochemistry*, 2005, 20(2):92-103, and Halstead S.B. *et al.*, *Vaccine*, 2005, 23:849-856, which support this.

The Examiner asserts that the guidance in the specification as to how to achieve delivery to target cells is general. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 883, 839; 166 USPQ 18, 24 (CCPA 1970); and MPEP 2164.03. Accordingly, what is known in the art provides evidence as to the question of predictability. Applicants respectfully submit that the references cited in the Office Action are not representative of the art of gene and siRNA delivery. The state of the art was sufficiently developed such that tools and methods for achieving the required inhibition were appreciated by the inventors, taught in the patent application, and available to those of ordinary skill in the art. Thus, Applicants submit that the patent application contains sufficient disclosure to enable one of ordinary skill in the art to carry out the methods of the invention without undue experimentation.

Submitted herewith for the Examiner's consideration are Milhavet O. *et al.*, *Pharmacol. Rev.*, 2003, Dec., 55(4):629-648; Agrawal N. *et al.*, *Microbiol. Mol., Biol. Rev.*, 2003, Dec., 67(4):657-685); Kim V.N. *et al.*, *J. Korean Med. Sci.*, 2003, 18:309-318; Gitlin L. and Andino, *J. Virol.*, 2003, 77(13):7159-7165; Coburn G.A. and Cullen, *J. Antimicrobial Chemotherapy*, 2003, 51:753-756; Lieberman J. *et al.*, *Trends Mol. Med.*, 2003, 9(9):397-403; Reich S.J. *et al.*, *Molecular Vision*, 2003, 9:210-216; Scherr M. *et al.*, *Oligonucleotides*, 2003, 13:353-363; and Song E. *et al.*, *Nature Medicine*, 2003, 9(3):347-351, which describe gene silencing using interfering RNA *in vivo*.

As shown by the Milhavet *et al.*, and Agrawal *et al.*, and the other documentary evidence submitted herewith, many laboratories have had significant success in reducing endogenous and foreign gene expression in a large variety of cell types, using various RNA species and delivery methods (see, for example, Table 1, at pages 635-636 of Milhavet *et al.*). Inhibition of viral replication has been achieved *in vitro* and *in vivo* using interfering RNA-mediated gene silencing, as demonstrated by Coburn G.A. and Cullen, *J. Virol.*, 2002, 76(18):9225-9231; Lee M-T M. *et al.*, *J. Virol.*, 2003, 77(22):11964-11972; Qing Ge *et al.*, *PNAS*, 100(5):2718-2723; McCaffrey A.P. *et al.*, *Nature*, 2002, 418(6893):38-39; McCaffrey A.P. *et al.*, *Nat. Biotechnol.*, 2003, 21(6):639-644; Hu W.Y. *et al.*, *Curr. Biol.*, 2002, 12(15):1301-1311; and Gitlin L. *et al.*, 2002, 418(6896):430-434,

which are submitted herewith. In addition, before and after the subject application was filed, RNAi-mediated gene silencing *in vivo* has been demonstrated in non-human primates (Tolentino M.J. *et al.*, *Retina*, 2004, 24:132-138; Zimmermann T.S. *et al.*, *Nature*, 2006, 441(7089):111-114, which are submitted herewith).

The standard for determining whether the specification meets the enablement requirement was articulated in the Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which framed the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). There are several factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The Examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *In re Wands*, 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407.

A conclusion of lack of enablement means that, based on the evidence regarding each of the relevant factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Applicants note that the Examiner has not indicated what information or guidance is allegedly lacking in Applicants' disclosure or the prior art that must be provided in order for one of ordinary skill in the art to carry out the claimed method without the need for undue experimentation.

The Examiner asserts that the specification lacks a working example. As indicated in MPEP 2164.02, an *in vitro* example in the specification, in effect, constitutes a working example if that example correlates with the claimed method of use. Since the initial burden is on the Examiner to give reasons for the lack of enablement, the Examiner must also give reasons for a conclusion of lack

of correlation for an *in vitro* example. A rigorous or an invariable exact correlation is not required. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985) and MPEP 2164.02. The *in vitro* data presented in the subject specification is reasonably predictive of *in vivo* efficacy in reducing DV gene expression in a mammalian animal host, as the ordinarily skilled artisan, having the benefit of the teachings of the subject specification, would expect that the claimed vector will have *in vivo* efficacy.

Applicants respectfully submit that, in view of the disclosure of the subject specification as originally filed, which demonstrates that DV gene inhibition can be achieved and would be of benefit, for example, in inhibiting DV infection, methods for reducing DV gene expression using the recited vectors are fully enabled. Inhibition of gene expression using nucleic acid inhibitors of genes has been demonstrated in animal models of disease states. All that is required by the patent laws is that a "reasonable correlation" exist between the scope of the claims and the scope of enablement. *In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) and MPEP 2164.02. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 224 USPQ 739, 747 (Fed. Cir. 1985):

> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

Applicants respectfully submit that the data within the specification is reasonably predictive of inhibition of DV genes in mammalian animal hosts *in vivo*. As such, the pending claims are commensurate in scope with the experimental findings of the instant disclosure and enabled thereby.

Accordingly, Applicants respectfully submit that, given the teaching of the specification and the state of the art in gene suppression using agents such as siRNA, one of ordinary skill in the art could carry out the claimed methods using the recited vectors, without the need for undue experimentation. In view of the foregoing remarks, and the documentary evidence submitted herewith, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of the Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, the Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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Attachments: Request for Continued Examination (RCE) under 37 CFR §1.114
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